MINERAL METABOLISM*

JOSEPH C. AUB
Harvard Medical School

In no constituents of the body is the so-called "homeostasis" of Cannon more strikingly maintained than in the inorganic salts. These salts are composed of a number of bases and a number of acid radicles, which respond in an accurate, coordinated way so that they balance each other, not only to maintain the pH of the body but also to help maintain the constant osmotic pressure of tissue fluids. In the body, because of the great efficiency of the normal kidney, an excessive intake of either acid or base can be readily eliminated. By such means as this the body cells are bathed by a solution which remains extraordinarily constant in salt content. Probably the content of no substance remains so constant in the body tissues as do the inorganic bases. Normally at the level of 150-160 milliequivalents it varies only very rarely as much as 10 milliequivalents from the normal. It is obviously of enormous importance to keep the bases in the blood at a constant level, a level which is not far removed from the concentration of base in sea water at the time when we are supposed to have emerged from it. In order to maintain this constant level it is essential that water and salts should fluctuate together, so the generalization can be made that in disease, when excess base is lost by excretion, water is also lost and dehydration follows; when base is retained, so also is water, and edema results.

One of the striking and unexplained phenomena of the salts in the body is the distribution of base. Sodium is the predominating base of all the fluids outside of the cells, while potassium predominates inside all of the cells. As a result, when fluids are lost from the body it is largely

* Delivered October 25, 1933.

sodium salts which are excreted. This is well illustrated by the fluid losses in burns, diarrhoea, or excessive vomiting. Here the body becomes depleted of its sodium salts so that they must be replenished.

On the contrary, when body cells are broken down there is a depletion of potassium salts. This may be seen in starvation, where breakdown of tissue is associated with a mounting elimination of potassium through the kidney. At the same time, the excretion of sodium from extra-

TABLE I.

URINARY EXCRETION DURING FASTING*

Days of Fast	Calcium gms.	Potassium gms.	Sodium gms.
2-4	.24	1.37	.93
5-6	.27	1.45	.28
10-11	.22	1.01	.10
18-19	.25	.68	.05
24-25	.17	.79	.06
30-31	.14	.61	.05

cellular fluids falls to a very low level so that the total base content of the blood plasma remains constant (Gamble, Ross, and Tisdall[1]) even after a prolonged fast. Remembering that it is essential to health to maintain the normal salt concentration in the body, as well as to maintain a normal volume of blood, let us see what happens superficially in two diseases in which these levels are sorely strained, namely, intestinal obstruction and nephritis.

The work of Gamble and McIver[2] has taught us much in regard to the effects of intestinal obstruction. The gastric juice contains not only a large amount of hydrochloric acid but also a considerable amount of sodium. Bile and pancreatic juice also have as much sodium in them as has the blood serum and they are alkaline in reaction. This large amount of base and of chlorine ions, which is poured into the intestinal tract, is reabsorbed in health, but in certain clinical conditions they may be lost. Thus, ex-

*Taken from Benedict, F. G., A Study of Prolonged Fasting, Carnegie Institution of Washington, 1915.

cessive vomiting with or without intestinal obstruction, or bile fistulae, or even severe diarrhoeas are all associated with a loss of base and of chlorine. The importance of these secretions in regard to fluid as well as salts is well illustrated in the work of Rowntree.

TABLE II.

AN ESTIMATE OF THE RELATIVE DAILY VALUES OF SECRETIONS POURED INTO THE INTESTINAL TRACT OF MAN*

	cc.
Saliva	1500
Gastric juice	2500
Bile	400
Pancreatic juice	600
Succus entericus	3000
	8000
Total blood plasma	3500

* Taken from Rowntree, L. G., *Physiol. Reviews*, 1922, II, 116.

It is dramatically evident, when one compares the total volume of blood plasma to the daily volume of intestinal secretions that a precarious situation may result from the loss to the body of these secretions. If the vomiting is gastric, there is more chlorine lost than base, if it involves the bile and pancreatic secretion there is apt to be an excess of base lost in the fluid.

So as not to complicate the problem too much, let us consider pyloric obstruction alone, which has been well studied by Gamble[2]. The loss in this condition is largely hydrochloric acid and sodium. This loss may be great and is complicated by the obvious inability of the body to replace this loss by eating. There follows a greater loss of chlorine than of sodium. As a result, there is a tendency to an alkalosis with the resulting picture of "gastric tetany." Chlorides in the blood may fall to less than half the normal concentration (McVicar, C. S.[3]), a loss which is far greater than that of base. The body can stand this disproportionate loss very poorly and, therefore, gets back to a relative balance by excreting more base by urine. The result is a very marked fall in base as well as chlorides

in the plasma. This condition demonstrates dramatically how essential are inorganic salts to health, for there is a rapid appearance of the picture of intense dehydration, diminished urinary output, nitrogen retention, with an eventual collapse and death. The treatment for it is simple and is the same for all of the diseases in which excessive intestinal contents are lost: sodium chloride and water in adequate amounts. By adequate amounts is meant enough to cause a good flow of urine so that any excess of chlorides or of base are separately dealt with by the kidneys. No other treatment seems an adequate substitute. Water alone, or soda bicarbonate alone, or glucose (Walters, W. and Bollman, J. L.[4]) or ammonium chloride are not satisfactory (Gamble, J. L. and Ross, L. G.[5]), for all three of the essential substances which have been lost must be replaced, and water, sodium, and chloride must be given. With adequate kidneys, a fairly rapid adjustment is made and the components which are given in excess are excreted while those sorely needed by the body are retained. A similar situation has recently been demonstrated in Addison's disease (Harrop[6]).

The lavish loss of water and sodium and chloride, which may result from intestinal abnormalities, is in great contrast to the work of the kidneys. In the secretion of urine by normal kidneys, each inorganic component of the plasma is excreted only when present in excess. As a result, the normal kidney maintains a quite constant environment for the body cells, as long as the various constituents are adequately supplied. With kidney damage, however, the accuracy of the mechanism may be lost and salts and water may be retained or excreted in excess. This is soon followed by symptoms.

In the edema of nephrosis, the reduction of the plasma proteins plays a most important part which cannot be discussed this evening. However, the inorganic salts are also seriously involved for where there is edema there is retention not only of water but also of sodium and chloride. We

speak clinically of chloride retention, meaning retention of inorganic salts. This term is used because of the fact that the chemical analysis for chlorides is simpler than that for base. It is probable that sodium has far more to do with edema than has chloride retention. Good evidence for this lies in the tendency to retain water when sodium bicarbonate is given and to produce diuresis when ammonium chloride is administered. All of the retained salts and water stay in the tissues, for Van Slyke[7] has shown that the volume of blood plasma in edematous patients is quite normal, while Peters has shown that the total base in the blood plasma is usually lower than normal (Peters, J. P., Wakeman, A. M., Eisenman, A. J., and Lee, C.[8]).

The retention of sodium, chloride, and water is not the invariable result of kidney damage. In fact, in the advanced stages of nephritis, where large quantities of dilute urine are excreted, sodium and chloride may be washed from the body. Under such conditions, Peters[8] has found that the total content, as well as concentration, of sodium salts in the body may be definitely reduced and with this, of course, is associated dehydration.

From the point of view of these findings, it becomes obvious that the treatment of nephritis will vary according to the condition of the body fluids. In patients with edema and stored sodium chloride, salt intake should obviously be restricted, but in nephritics where dehydration from polyuria is marked the ingestion of adequate salt is indicated and needed.

What has been said, in both of the abnormalities discussed, suffices to bring out the fact that the primary inorganic salt involvement in volume changes of extracellular fluid has to do with abnormalities of sodium and of chloride. In changes which involve body cells, however, as in starvation, the important loss from the body is the predominating base of tissue cells, potassium.

So far, this discussion has referred to the salts of the soft body tissues. These salts exist only in the necessary concentration in the active protoplasm of cells and the fluid which bathes them. There is no large storehouse of these salts. If they are lost from the body the sole source of replenishment is from food or medication. However, there is one large storehouse for inorganic salts from which, in time of need, large quantities of base and acid can be drawn. The bones, in this regard, resemble the fat storehouses in the caloric requirements of the organism. The role of calcium and of phosphorus is, therefore, of interest in two ways: first, in their deposit in the bones and, secondly, in the liberation from the bones to satisfy the needs of the organism as a whole.

In the metabolism of bone we clinicians are apt to speak too simply of calcium metabolism. It must be remembered that phosphates are fully as important as is calcium. This is quite well recognized now in rickets where an inadequate phosphate intake may be of prime importance. An excellent example of this is found in the work of Theiler[9]. He studied the disease of Lambsiekte in cattle on the South African veldt. These herbivorous animals had the extraordinary habit of eating the bones of dead animals of their own kind. Theiler found that this proved lethal because of a botulinus infection which was spread by this osteophagia. Why should herbivorous animals eat bones? This he found was due to a deficiency of phosphorus in the grasses used for grazing, and, by making adequate amounts of inorganic phosphates available to the cattle, he promptly caused osteophagia to cease. This discovery was of great economic, as well as scientific value. It serves as an excellent example of the need of the body for phosphates, a radicle equally as important as calcium, to which it is so closely related.

Calcium and phosphorus metabolism differ from the other inorganic salts because they are continuously going in and out of the bones, and are continuously being excreted, even in starvation. If the normal level of calcium

in the blood is changed, effects are seen in muscle tone. A low blood calcium, below 7 mg. per cent, is associated with an increased neuromuscular irritability, or tetany. A high blood calcium leads to low muscle tone, an increased calcium excretion, and abnormal changes in the bones and kidneys.

The maintenance of this normal calcium level is more complicated than that for sodium, for several factors other than the kidney affect it. First, there must be adequate absorption of calcium. This is obviously difficult and in certain diseases like steatorrhoea or Gee's disease it cannot be adequately accomplished. In this digestive disease there is difficulty in absorbing fats and soaps, resulting in the excretion of insoluble calcium soaps in the bulky diarrhoea, thus preventing the absorption of calcium into the body. The result is a gradual thinning of the bones with the development of osteomalacia, and an eventual fall of the blood calcium and tetany. Vitamin D improves the absorption of calcium from the intestine and in very large quantities will relieve this condition.

Except for this effect of Vitamin D, little is known of the factors which influence the absorption of calcium. Once absorbed, calcium may either be deposited in the bones or excreted. The retention in the bones may be large, certainly as much as a gram a day for short periods. This storehouse, however, is not an inert deposit, for the bones are continuously giving up and replacing their salts, and there is good evidence that calcium probably leaves one part of the bones to be redeposited in other parts. How this calcium is deposited and liberated is not always clear. Certainly, there are cells—the osteoblasts, associated with new bone formation; and the osteoclasts, associated with the absorption of bone tissue. Osteoclasts are described in bone which is being depleted by parathyroid hormone[10], and in hyperthyroidism[11]. It is not known whether bone salts can be absorbed or deposited without the presence of these cells. It is hard to believe that the ingestion of acid salts, which increase calcium excretion, causes this

liberation from bones by the activity of osteoclasts, but this problem is not yet settled. At any rate, bone salts are easily pulled from or deposited in the bones. The chief seat of this calcium storehouse is in the bone trabeculae near the epiphyses. These trabeculae can easily be depleted by a low calcium diet and can be replaced by increasing the calcium intake. The bone shafts are less seriously involved, though recent work has indicated that they may also show microscopic evidence of absorption in hyperparathyroidism and hyperthyroidism[10, 11].

What are the known factors which influence this store and influence the level of calcium in the blood? They include internal secretions, vitamins, and foods.

The parathyroid glands are probably the most important of these factors in the normal regulation of the body calcium. Their primary influence seems to be upon the level of blood calcium and phosphorus. From a normal level of 10 mg. per cent, the calcium falls after parathyroid extirpation to 4 or 5 mg. per cent. Signs of intense tetany develop in about twenty hours, when the blood calcium has fallen below 7 mg. per cent.

The lowered serum calcium causes intense irritability of the neuromuscular mechanism and the laryngeal and muscular spasms and generalized convulsions are evidence of this. Calcium excretion on a low calcium intake falls to a minimum. When parathormone, the active principle of the parathyroid gland, is injected intramuscularly there is a latent period of four hours, after which the blood calcium rises and tetany disappears for approximately twenty hours.

If an overdose of parathormone is given, or with an overacting parathyroid adenoma, the blood calcium rises above normal and may even reach 20 mg. per cent. This condition of hyperparathyroidism is being described to you later by Dr. Jaffe. Here, therefore, it need only be said that the amount of calcium absorbed from the intestines is not influenced by parathormone and that the increased

calcium in the blood and urine, resulting from overdoses of the hormone, comes from the bones. This is evident from the experimental work of Jaffe and Bodansky[10], which showed bone changes even with probably adequate calcium in the food. With very high calcium diets, however, these cases can be maintained in calcium equilibrium[12] or even a positive balance. What the bones would then show I do not know. It is interesting that an immunity develops towards commercial parathormone, prepared from cattle, so that after several weeks or months of use the blood calcium sinks back to its original level. This must be an immunity to a foreign protein, for no such immunity follows the oversecretion of a parathyroid tumor. One such case, of twelve years' duration, is known to have maintained a high blood calcium for the last seven years of the disease.

The action of parathormone is mimicked in every way by large doses of Vitamin D. This was first pointed out, I think, by Porges[13], who cured a chronic case of tetany by means of viosterol. Taylor, Weld, Branion, and Kay[14] also showed this close relationship and recently Kozelka, Hart and Bohstedt[15] have shown that parathyroidectomized puppies can reach maturity and can raise normal offspring by the use of large doses of viosterol. The differences seem to be that viosterol aids in the absorption of calcium from the intestine, and its effect lasts for days, while parathormone lasts for only a matter of hours. It is important to remember that a high blood calcium level is nearly always due to overactivity of the parathyroid glands or to overdosage with vitamin D. I think there is also a very rare case associated with an excess of protein in the blood. A low blood calcium level means parathyroid or vitamin D deficiency, or a deficient calcium absorption. Calcium is also somewhat reduced when plasma proteins are low (Peters). Although the parathyroids and vitamin D are the factors which affect *blood* levels of calcium, they are not the only influences which affect calcium metabolism. Abnormal calcium *excretion* can be stimulated by other

means. The thyroid hormone is an important influence, since oversecretion of the thyroid gland increases the excretion of calcium enormously, while in myxedema the demands upon calcium stores are markedly reduced[16]. The thyroid secretion exerts no effect upon the normal level of blood calcium. Its action rather seems to stimulate the catabolism of bone, which results in excessive excretion.

An acid diet is the last factor I want to speak of, for a large excess of acid can increase the excretion of calcium approximately as does parathormone, but this factor again does not appreciably affect levels in the blood[17].

Table III shows the various laboratory combinations which are important in diagnosis.

TABLE III.

ANALYTICAL FINDINGS IN VARIOUS TETANIES AND RELATED DISORDERS

DISEASES	BLOOD PLASMA VALUES				EXCRETION DURING LOW CALCIUM DIET			
	Calcium	Phosphorus	pH	Phosphatase*	Urine Ca	Urine P	Feces Ca	Feces P
Tetany due to Parathyroid deficiency	low	high	normal		low	low	normal	normal
Hyperparathyroidism	high	low	normal	high	high	high	normal	normal
Steatorrhea—Difficulty in absorbing calcium from the intestines	normal or low	low	normal	normal or slightly high	low	high	high	normal
Osteomalacia from Deficiencies and Rachitis	normal or low	low	normal	high	low	low	low	low
Hyperthyroidism	normal	normal	normal	high	very high	very high	high	high
Paget's Disease (Osteitis Deformans)	normal	normal	normal	very high	No marked variation			
Gastric Tetany	normal	normal	increased					

* See Kay, Physiological Reviews.

From these factors the treatment of low calcium tetany is clear.

1. A high calcium diet, possibly with added acid salts like ammonium chloride.
2. Intravenous or intramuscular use of calcium gluconate for immediate effect. For more lasting effects which, however, are not obtained for some hours, one should employ No. 3.
3. Large doses of viosterol to raise the blood calcium level. Because no immunity develops to this, it is preferable to No. 4.
4. Parathormone.
5. Thyroid medication, which is well worth remembering.

To practitioners of medicine, I cannot abstain from mentioning the importance of calcium during pregnancy. It has been shown by Schmidt[18] and others that an enormous amount of calcium can be stored in the bones during pregnancy. That it is important to accomplish this by a high calcium diet throughout pregnancy is self evident, when one realizes that a negative calcium balance can probably not be avoided throughout the period of lactation. Further evidence of strain upon the calcium metabolism is indicated by the interesting work of Kozelka, Hart, and Bohstedt[15]. Their parathyroidectomized dogs could be maintained with a normal blood calcium by daily doses of 14 rat units of vitamin D. During pregnancy, however, 4,000 to 26,000 were required and during lactation as many as 66,000 rat units were necessary. This extraordinary demand implies some mechanism which we do not yet understand.

It is also important to realize that several heavy metals behave in the body approximately as does calcium. Lead[19], mercury[20], and radium[21] are influenced by the same procedures that influence calcium. They are stored in the bones and are liberated from this storehouse in increased amounts when calcium is liberated. This offers a method

of treatment which allows the most readily available of these metals to be pulled from the bones and excreted[19]. The remainder is excreted very slowly, just as is calcium.

What is the interrelationship in body fluids of these ions which are stored, such as calcium and phosphates, to those which have no storehouse, like sodium and chloride? In the first place, the concentration of the calcium and phosphorus is relatively very small. Variations which double their concentration would not affect the total level of acid or base in the plasma more than occurs physiologically, and there does not appear to be much readjustment in other ions to such a change. These ions with low concentration in body fluids, may therefore cause dramatic signs and symptoms quite independently of other ions. Total base or chloride excretion is not influenced by the giving of parathormone, which dramatically increases the calcium and phosphorus elimination[22]. Thus, there is a good deal of independence of excretion of each of these substances and yet they remain closely related as a whole, keeping an accurate balance between acids and bases to maintain the normal pH of the body, and keeping normal the osmotic pressure and the inorganic salt environment—a group of substances which maintain a remarkable equilibrium in spite of the possibility of individual divergence from the norm.

BIBLIOGRAPHY

1. Gamble, J. L., Ross, G. S., and Tisdall, F. F., *J. Biol. Chem.*, 57: 633, 1923.
2. Gamble, J. L., and McIver, M. S., *J. Exp. Med.*, 48: 837, 1928; and 48: 859, 1928.
3. McVicar, C. S., *Am. J. Med. Sci.*, 169: 224, 1925.
4. Walters, W., and Bollman, J. L., *Arch. Surg.*, 13: 578, 1926.
5. Gamble, J. L., and Ross, L. G., *J. Clin. Inv.*, 1: 403, 1925.
6. Harrop, G. A., Soffer, L. J., Ellsworth, R., and Trescher, J. H., *J. Exp. Med.*, 58, 17, 1933.
7. Linder, G. C., Lundsgaard, C., Van Slyke, D. D., and Stillman, F., *J. Exp. Med.*, 39: 921, 1924.

8. Peters, J. P., Wakeman, A. M., Eisenman, A. J., and Lee, C., *J. Clin. Inv.*, 6: 517, 1929.
9. Theiler, Sir Arnold, Lambsiekte in Cattle in South Africa, Dept. of Agriculture, Union of South Africa, January, 1927.
10. Jaffe, Henry L., and Bodansky, Aaron, *J. Exp. Med.*, 52: 669, 1930.
11. Hunter, Donald, *Quarterly Journal of Med.*, 24: 394, 1931.
12. Bauer, W., Albright, F., and Aub, J. C., *J. Clin. Inv.* 8: 229, 1930.
13. Porges, Otto—Personal communication.
14. Taylor, N. B., Weld, C. B., Branion, H. D., and Kay, H. D., *Canadian Med. Assoc. Jour.*, 24: 763, 1931 and 25: 20, 1931.
15. Kozelka, F. L., Hart, E. B., and Bohstedt, G., *J. Biol. Chem.*, 100: 715, 1933.
16. Aub, J. C., Bauer, W., Heath, C., and Ropes, M., *J. Clin. Inv.*, 7: 97, 1929.
17. Farquharson, R. F., Salter, W. T., Tibbetts, D. M., and Aub, J. C., *J. Clin. Inv.*, 10: 221, 1931.
18. Goss, Harold, and Schmidt, Carl L. A., *J. Biol. Chem.*, 86: 417, 1930.
19. Aub, J. C., Fairhall, L. T., Minot, A. S., and Reznikoff, P., Lead Monograph, Williams and Wilkins Co., 1926.
20. Young, A. G., Taylor, F. H. L., and Merritt, H. H., *Arch. Dermatology and Syphilology*, 21: 539, 1930.
21. Flinn, F. B., and Seidlin, S. M., *Bulletin of the Johns Hopkins Hospital*, 45: 269, 1929.
Flinn, F. B., *J. A. M. A.*, 96: 1763, 1931.
22. Albright, F., Bauer, W., Ropes, M., and Aub, J. C., *J. Clin. Inv.*, 7: 139, 1929.

PROCEEDINGS OF ACADEMY MEETINGS

JANUARY

ANNUAL MEETING—January 4

I. EXECUTIVE SESSION—Reading of the Minutes; Election of Fellows and Members; Presentation of Diplomas; Announcement re: Amendments to By-Laws introduced at the Stated Meeting of December 7, 1933.

II. PRESENTATION OF ANNUAL REPORTS—(Read by title) The Council, The Trustees, The Treasurer, Committees.

III. ADDRESSES OF THE EVENING—a. Activities of the past year, Bernard Sachs; b. Presentation of Thomas W. Salmon Memorial Committee Report and portrait of Dr. Salmon, C. C. Burlingame; c. *Symposium on Encephalitis* with especial reference to the St. Louis outbreak; 1. Clinical and research aspects of the St. Louis epidemic, Ralph S. Muckenfuss, St. Louis; 2. Epidemiology, James P. Leake, Washington; 3. Recent research in the disease, Leslie T. Webster; 4. Clinical observations, Josephine B. Neal; 5. The importance of differential diagnosis, Frederick Tilney; 6. Discussion and summary, Thomas M. Rivers.